iv) purified filamentous hemagglutinin is utilized;

v) inactivated poliovirus is utilized;

Arminjon *et al.* is silent with regard to all five limitations and, therefore, does not provide the requisite suggestion or motivation to make the presently claimed invention. Petre *et al.* is likewise silent on most points above and both references fail to provide the motivation to combine. Nevertheless, such combination fails to provide all limitations of the present invention and thus cannot render it obvious. Specific arguments for each assertion of the Advisory Action of May 15, 2002 are provided below.

The Advisory Action of May 15, 2002 asserts in its explanatory note that "the metes and bounds of 'effective amount' are unclear" and that the "claims should recite endpoints that indicate that an effective amount has been administered." Applicant respectfully points out the description of the accepted definition of seroprotection within the vaccinology community found in the specification:

> In Table 4, the criteria for seroprotection correspond to the reference commonly admitted by the vaccinology community for each component in terms of expected antibody response obtained after a primary immunization consisting of three doses given 1 to 2 months apart or after a booster immunization given about one year after the first immunization. The criterion for seroprotection for the PT and FHA antigens are 4-fold rise between pre and post primary series titers and post fourth dose titers. SPR is the seroprotection rate and corresponds to the percentage of subjects fulfilling the criterion of response. *See page 19, lines 21-27 and Table 4.*

Table 6 also provides a concise list of what is considered an effective amount, or the accepted definition of seroprotection as well as results from the instant invention. In addition, further guidance is provided in the form of dosage ranges for each component of the multivalent vaccine, *inter alia*, page 9, lines 11-29, page 13, lines 11-32 and page 14, lines 21-26. Thus, applicants respectfully contend that the instant application clearly describes what the metes and bounds of 'effective amount' are and that endpoints indicative of an effective amount are recited.

Furthermore, "effective amount" language as presently employed has been accepted by the courts. The Court of Customs and Patent Appeals stated that "'effective amount' admirably states what is to be derived from disclosure of specification as to amount." See *In re Caldwell, 138 USPQ 243, 247 (CCPA 1963)*; *In re Halleck, 164 USPQ 647, 649 (CCPA 1970)* (The functional term 'an effective

amount...for growth stimulation' is not objectionable where the *amount* as such is not critical and its use has been approved in many cases). For the foregoing reasons, applicants respectfully request the withdrawal of the rejection based on the alleged lack of clarity regarding the metes and bounds of an "effective amount".

The Advisory Action also asserts that "the prior art of record shows that methods of adsorbing diphtheria and tetanus toxoids to aluminum salts were known, see WO 93/24148" and "therefore, it would have been obvious to Arminjon to use the well known methods (such as those described in WO 93/24148) to modify the vaccine formula to improve stability." A problem addressed by the presently claimed invention is the instability of the HiB valence. Petre *et al.* circumvent the instability of the HiB valence by extemporaneous addition of it to the vaccine just prior to vaccine administration, specifically stating that the HiB antigen is "used extemporaneously by formulating the vaccine just prior to administration." See page 4, lines 18-19. Petre *et al.* does not provide any motivation to modify the method disclosed therein, particularly in a manner leading to the presently claimed method. That is, Petre *et al.* does not suggest (a) adsorbing the tetanus toxoid or diphtheria toxoid onto an aluminum salt and (b) preparing the HiB conjugate in a phosphate buffer, and then mixing each with the other components.

Petre *et al.* further fails to provide any teachings of a reasonable expectation of success. Petre *et al.* not only fails to suggest adsorbing the tetanus toxoid or diphtheria toxoid onto an aluminum salt, preparing the HiB conjugate in a phosphate buffer, and then mixing each with the other components, it specifically teaches away from other aspects of the present invention. Petre *et al.* specifically states that "when AH-adsorbed [aluminum hydroxide-adsorbed] HBsAg is used in combination with other vaccines in a combined formulation there is a substantial decrease of the immune response to HBsAg, resulting in lower or insufficient seroprotection after vaccination." See Petre *et al.*, page 1, lines 28-31. In marked contrast, the Examples of the present specification establish that vaccines according to the invention do not suffer from the problem of antigenic competition in which the immunogenicity of the individual components of the multivalent vaccine is impaired by the presence of the other components of the composition, thus suppressing the seroprotection of some or all components of the vaccine upon administration. HBsAg, in particular, does not demonstrate Petre *et al.*'s recited problems, with seroprotection greater than 90% (and greater than 98% upon booster;

see Table 6) offered by the present invention which utilizes an adjuvant specifically taught against by Petre *et al.* in a multivalent vaccine.

To further emphasize the apparent importance of its point, Petre *et al.* is even more explicit asserting, "There appears, however, to be no appreciation of the need to avoid aluminum hydroxide as an adjuvant for a multivalent vaccine comprising HBsAg."[1] *See* page 2, lines 4-6. Thus, Petre *et al.* once again specifically teaches against the use of aluminum hydroxide as an adjuvant for HBsAg-containing vaccines in direct opposition to the present invention. Specific teachings of the present invention can be found at page 9, lines 31-32, which states, "In addition, the vaccine may also comprise an adjuvant, particularly aluminum hydroxide" and, *inter alia*, page 9, lines 9-10, page 16, lines 34-38 and page 17, lines 1-27. In addition, the results outlined in Tables 4 and 6 illustrate that vaccines prepared according to the present invention do not suffer from the deficiencies described by Petre *et al.* for HBsAg-containing vaccines utilizing aluminum hydroxide adjuvants. Thus, the distinct methods claimed in the instant application yield surprising results that are significantly different than those of Petre *et al.* and, for the reasons described above, Petre *et al.* fails to anticipate or render obvious the present invention. Indeed, applicant's teachings and results generated in the environment of the disclosure of Petre *et al.* contradicts the Advisory Action's statement that "one would have been motivated by the well known concept of stabilization of vaccine antigens, evidenced in WO 93/24148" and that "one would have had reasonable expectation of success that adsorption would result in stability of the vaccine compounds."

In summary, Arminjon *et al.* and Petre *et al.* fail to teach or suggest all of the limitations of the present claims and, therefore, cannot render obvious the invention of the present claims. In view of all of the foregoing, the applicants respectfully request reconsideration and withdrawal of this § 103(a) rejection.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

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[1] Applicants note, however, that a commercially available vaccine, Engerix (SmithKline), which comprised hepatitis B surface antigen adjuvanted with aluminum hydroxide, was publicly available before the priority filing of the instant application.

Amended Claims

Claims 21, 36 and 37 have been amended to more particularly point out and distinctly claim the subject matter that applicants regard as the invention. Applicants note that claims 21, 36 and 37, as originally filed, describe a patentable invention, but have amended said claims to promote clarity.

Conclusion

Applicants submit that the present application is now in condition for allowance, and notice to that effect is hereby requested. Should the Examiner feel that further dialog would advance the subject application to issuance, she is invited to telephone the undersigned at any time.

Respectfully submitted,

Date: August 2, 2002

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Redlined Version of Amended Claims

21. (Twice Amended) A method for preparing a stabilized multi-component vaccine, the method comprising mixing at least:

a) pertussis toxoid and filamentous hemagglutinin in purified form,

b) tetanus toxoid,

c) diphtheria toxoid,

d) inactivated polio virus,

e) a conjugate of a carrier molecule selected from tetanus toxoid and diphtheria toxoid and a capsular polysaccharide of *Haemophilus influenzae* type B, and

f) an aluminum salt,

wherein tetanus toxoid and diphtheria toxoid are adsorbed onto the aluminum salt before being mixed with the other components and the conjugate is prepared in a phosphate buffer solution before being mixed with the other components.

36. (Twice Amended) A method for conferring protection in a host against disease caused by *Bordetella pertussis, Clostridium tetanii, Corynebacterium diphtheriae, Haemophilus influenzae, Poliovirus* and/or *Hepatitis B virus* ~~using~~ comprising administering an effective amount of a multi-component vaccine obtained by the method of claim 27.

37. (Twice Amended) A method of immunizing a human host against disease caused by infection by *Bordetella pertussis, Clostridium tetanii, Corynebacterium diphtheriae, Haemophilus influenzae, Poliovirus,* and/or *Hepatitis B virus*, which method comprises administering to the host an effective amount of a multi-component vaccine obtained by the method of claim 27.